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Editorial

Bypassing the bottleneck: Gamma-glutamylcysteine supplementation for brain glutathione enrichment in Alzheimer's disease

Journal of Alzheimer's Disease
1–8
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DOI: 10.1177/13872877261474009
journals.sagepub.com/home/alz



Pravat K. Mandal[1,2], George Perry[3], Joseph C. Maroon[1], Patricia Corby[4], Riddhi Patira[5] and Oscar L. Lopez[5,6]

Abstract

Alzheimer's disease (AD) is a major neurodegenerative disorder affecting more than 7 million Americans. Extensive studies have identified various factors associated with the development of AD, but the actual cause remains unknown. Transgenic mouse model and human studies strongly indicate that oxidative stress precedes amyloid-β plaque formation and tau phosphorylation in AD. GSH loss itself raises the Abeta42/Abeta40 ratio and promotes tau aggregation, placing GSH depletion upstream of classical AD pathology. Subsequently, the role of the master antioxidant, glutathione (GSH), came into focus for brain GSH level enrichment through supplementation with γ-glutamylcysteine (GGC), the immediate precursor of GSH. We present that GGC has an excellent safety record and bioavailability. GGC is a strong candidate to investigate for brain GSH enrichment (target engagement hippocampus, anterior cingulate cortex etc.) and subsequent cognitive enhancement for patients with mild cognitive impairment (MCI).

Keywords

antioxidant, brain imaging, clinical trial, enrichment, gamma-glutamylcysteine, glutathione, GSH conformers, magnetic resonance spectroscopy, MEGA-PRESS, mild cognitive impairment

Received: 7 March 2026; accepted: 15 July 2026

Introduction

Alzheimer's disease (AD) is a progressive neurological disorder that causes gradual deterioration of cognitive function and activities of daily living. As per the April 2025 Alzheimer's Association report, an estimated 7.2 million Americans (age ≥65 years) live with AD dementia. There is no cure for AD as the exact cause is not yet known. There are two dominant AD hypotheses: the amyloid-β (Aβ) cascade[1] and tau propagation[2] have been considered pivotal in its pathogenesis for the past three and a half decades. Existing medications provide only temporary symptomatic relief[2] and no effective disease reversal.[3–5] Recently approved anti-amyloid drugs also have a high incidence of amyloid-related brain imaging abnormalities which include microhemorrhages and cerebral edema.[6,7]

The first oxidative stress hypothesis in AD was reported in the early 1990s.[8–11] Pathological studies in AD patients indicated oxidative stress is the early disease process.[9,12–15] Prior work indicates that damage from iron mediated reactive oxygen species (ROS) generated through oxidative stress depletes the protective antioxidant glutathione (GSH) and is directly linked to the disease process. Ferroptosis is a non-caspase-dependent form of programmed cell death activated by oxidative stress induced by GSH depletion.[16] Using *in vivo* magnetic resonance spectroscopy (MRS) in

[1]Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA
[2]Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA
[3]Department of Neuroscience, Developmental and Regenerative Biology, University of Texas at San Antonio, San Antonio, TX, USA
[4]Department of Radiation Oncology & Clinical Trials Development & Operations, Health Sciences, University of Pittsburgh, Pittsburgh, PA, USA
[5]Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA
[6]Alzheimer's Disease Research Centre, University of Pittsburgh, Pittsburgh, PA, USA

Corresponding author:
Pravat K. Mandal, Research Professor, Department of Neurological Surgery and Radiology, University of Pittsburgh, Pittsburgh, PA 15213, USA.
Email: mandalpk@pitt.edu; mandalpk@upmc.edu; pravat.mandal@gmail.com

Handling Editor: Paula Moreira

cognitively normal (CN), mild cognitive impairment (MCI), and AD patients, significant GSH depletion in the hippocampus has been identified as an early biomarker of AD.[15,17–19] A prospective study found that higher plasma GSH levels at baseline were associated with a decreased risk of developing AD as well as better preservation of executive functioning longitudinally.[20]

Importance of GSH

GSH consists of three amino acid residues (glutamate, cysteine, and glycine) and acts as a master antioxidant. Most of the cellular GSH synthesis takes place in the cytosol (Figure 1). Homeostatic levels of GSH vary between tissue types. The liver contains the highest concentration of GSH in the body ranging from 5 to 10 mM;[21,22] Healthy brain is approximately ~2 mM, and plasma is approximately 3.2 ± 0.3 (μM/L).[23]

GSH is synthesized by the same pathway in the cytosol of all cell types, including neurons (Figure 1).[22,24] GSH acts directly as a ROS scavenger or indirectly as a cofactor for various enzymes such as glyoxylase-1, and glutathione peroxidase (GP).[25] GSH utilizes the active cysteine thiol (-SH) group, which attracts radicals. GSH neutralizes ROS through free non-enzymatic (radical scavenging) and enzymatic pathways. In non-enzymatic pathways, GSH reacts with free radicals such as superoxide radical ($.O_2^-$), nitric oxide, or hydroxyl ion (OH^-).[26,27] In enzymatic pathways, GSH functions as a reducing agent by donating an electron to H_2O_2 and subsequent formation of water and O_2 in the presence of GP enzyme.[28,29] To maintain the balance of redox homeostasis, oxidized GSH (GSSG) is converted back to GSH by glutathione reductase (GR) as indicated in Figure 1. Depletion of GSH could induce apoptosis, necrosis, or ferroptosis due to a decrease in GP activity. GSH exists in two conformations based on the surrounding microenvironments. The "closed form" GSH (dominant form) is identified by the existence of cysteine-Hβ peak at 2.80 ppm from nuclear magnetic resonance (NMR) spectra of GSH[30,31] as well as from *in vivo* MR spectroscopic data from the brain. The extended form of GSH is identified by the existence of cysteine-Hβ peak at 2.95 ppm from MR spectroscopy[19,31,32] and NMR data.[19] The depletion amount of GSH in the AD and MCI patients compared to cognitively normal person is as follows: (CN) 1.44 ± 0.27 mM; (MCI) 1.27 ± 0.30 mM; (AD) 1.17 ± 0.41 mM and $p = 0.026$.[33]

Pro-oxidant

The relationship between metal ions and oxidative stress is highly significant since the redox-active metals catalyze the production of most reactive radicals (hydroxyl radicals (•OH), etc.). AD is characterized by a severe imbalance in oxidant/antioxidant homeostasis, which impairs the antioxidant defense mechanism, leading to a significant elevation of oxidative stress and neurodegeneration.[15,35–37] Iron indirectly affects the lipid metabolism pathway in AD, which is regulated by apolipoprotein (ApoE), a risk factor for sporadic AD. Iron directly binds to the amyloidogenic proteins, influencing the cellular mitochondrial homeostasis. This causes aggregation of the Aβ in mitochondria and impairs their function, leading to impaired energy metabolism and excess ROS production.[38] Ferrous iron (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2) to produce highly reactive •OH through Fenton and Haber-Weiss reactions, thereby inducing ferroptosis, a form of cell death characterized by lipid peroxide buildup.[39] In autopsy studies as well as *in vivo* MRS and susceptibility studies in MCI patients, hippocampal GSH level (1.81 ± 0.35 mM) was depleted significantly compared to healthy control subject (2.17 ± 0.39 mM; $p = 0.04$) and in AD patients, hippocampal GSH level (1.58 ± 0.37 mM) depleted significantly ($p = <0.001$) compared to healthy controls.[40] The susceptibility level increases non-significantly in MCI patients compared to healthy controls ($p = 0.965$). However, the susceptibility values in AD patients (0.0140 ± 0.009 ppm) increased significantly compared to healthy controls (0.0064 ± 0.006 ppm) ($p = 0.029$).[40]

Glutathione in AD mice, autopsy, blood, and *in vivo* brain studies

The role of GSH in AD is an area of active research in various laboratories. The autopsy report of MCI patients provided valuable data pertaining to reduced GSH and GSSG forms. The ratio of GSH/GSSG of MCI patients was depleted significantly ($p = <0.05$) compared to healthy controls.[41] Animal model studies involving transgenic AD mice have shown that oxidative stress and metabolic changes in the hippocampal area precede intraneuronal Aβ and tau deposition in transgenic AD mice.[42,43] A two-year longitudinal study investigating blood plasma levels from MCI patients reported the mean plasma GSH level at the baseline (4.1 ± 2.5 ng/mL) is depleted significantly after 24 months (2.2 ± 2.7 ng/mL) ($p < 0.001$).[44] The depletion of GSH is positively correlated with Mini-Mental State Examination (MMSE) score.[44] Meta-analysis of GSH levels indicated that the subgroup of studies using MEGA-PRESS reported lower brain GSH in AD ($p < 0.001$) and MCI ($p < 0.001$) compared to controls.[45] A brief overview of involvement of GSH in AD is presented in Table 1.

GSH impact on AD

The bioavailability of GSH, N-acetyl cysteine (NAC), and γ-glutamylcysteine (GGC)

GSH is an essential antioxidant that protects against oxidative stress, but its oral bioavailability is below 1%.[47] NAC is

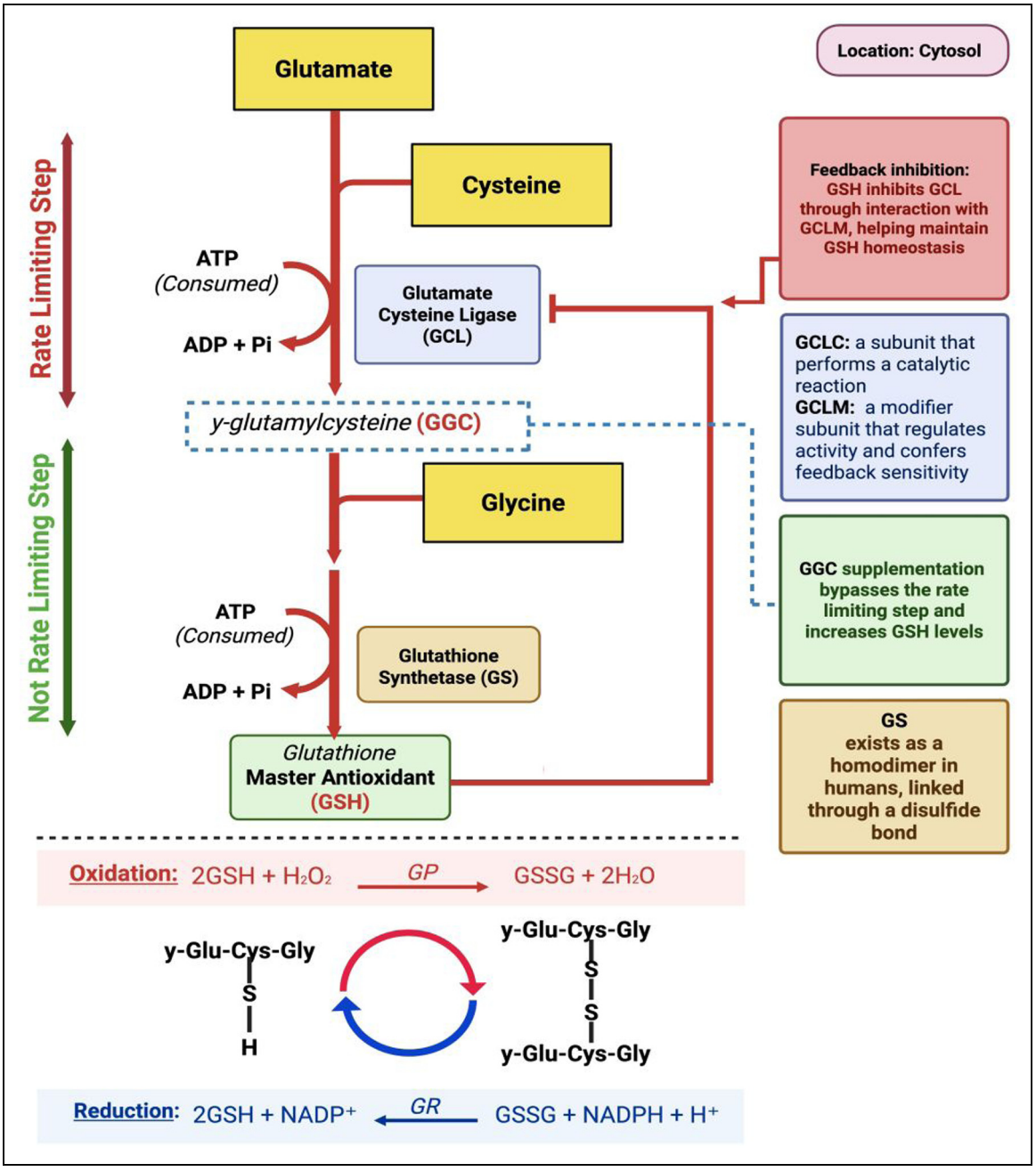


Figure 1. Glutathione (GSH) is present in all mammalian tissues and the biosynthesis of GSH occurs in the cytosol in a tightly regulated ATP dependent enzymatic step. Key determinants of GSH synthesis are the availability of cysteine and the activity of the rate-limiting enzyme, glutamate cysteine ligase (GCL). GCL enzyme consists of a glutamate–cysteine ligase catalytic (GCLC) subunit and a glutamate–cysteine ligase modifier (GCLM) subunit. GSH exerts non-allosteric feedback inhibition to GCL enzyme and acts as a competitive inhibitor. The second enzyme of GSH synthesis is the GSH synthetase (GS). GS is homodimer and generally has a higher specific activity than GCL.[34] Glutathione peroxidase (GP) converts GSH into oxidized GSH (GSSG) while neutralizing harmful hydrogen peroxide. GSSG is converted back to GSH by glutathione reductase (GR). Figure is generated using bioRender program (https://www.biorender.com/).

the precursor of cysteine, which is broken down in the liver and kidneys by the enzyme aminoacylase-1 and forms cysteine.[48] The bioavailability of free NAC is <10%.[48] A human study in healthy adults with oral supplementation of GGC demonstrated increased lymphocyte GSH above homeostatic levels indicating $53 \pm 47\%$ bioavailability and no reported toxicity.[49] Observed increased GSH levels through GGC administration to human astrocytes provide further support for its potential use as a therapeutic strategy to attenuate the oxidative stress effects in AD.[50]

Table 1. This table demonstrates that antioxidant GSH is depleted significantly in transgenic animal model studies. Data from autopsy as well as plasma, *in vivo* MRS studies from MCI and AD patients are presented.

Ser no	Transgenic animal model study	Autopsy Study (human)	Blood biomarker study (human)	Clinical study (*in vivo* imaging based) (patients)
1.	• Animal model studies have reported that oxidative stress in hippocampal area precedes intraneuronal Aβ and tau deposition in transgenic AD mice.[42] • Neuronal GSH depletion is an early step and elevates the $A\beta_{42}/A\beta_{40}$ ratio and tau aggregation in AD mice.[43]	• Significant ($p < 0.05$) depletion (49%) of GSH level in the cingulate cortex area in AD patients and iron level increment.[46] • Significant depletion of GSH level in MCI patients [41]	Longitudinal study reflects significant ($p = <0.001$) depletion of plasma GSH in the MCI patients.[44]	Significant GSH depletion of hippocampal ($p = <0.05$), ACC ($p < 0.05$) in MCI patients compared to healthy cognitively normal.[18,33,40]

Brain GSH enrichment: associated clinical studies involving GSH and NAC supplementation

In a natural process, each cell is designed to maintain its cytosolic homeostatic levels of GSH. The liver releases GSH into the blood plasma, which provides other cells in the body with a balanced source of the three amino acids (glutamate, cysteine, and glycine) used as substrates for the reassembly of GSH.[51] As indicated earlier, there is a significant depletion of GSH in MCI and AD patients, and GSH needs to be replenished to mitigate oxidative stress.

The breakdown of GSH is accomplished by γ-glutamyl transferase (GGT) enzyme, which is located on the outer leaf of the cell's plasma membrane. GGT cleaves GSH at the unique γ-glutamyl bond to form free glutamate and the dipeptide Cys-Gly, which is degraded further to Cys and Gly for transportation into cells via amino acid transporters.[52]

Oral supplementation of NAC undergoes a deacetylation reaction while in the digestive system and is converted into cysteine by removing the acetyl group. Cysteine is a critical component in GSH synthesis (Figure 1). There are several preclinical studies evaluating the impact of NAC on oxidative stress.[53] However, NAC supplementation in a human trial was found to be less impactful.[54]

Importance of GGC in health

GGC, a dipeptide, has an advantage compared to GSH or NAC as it is an immediate precursor to GSH.[55] GGC occurs in green beans, spinach, spices, and mustard. Higher levels of GGC occur in bovine milk, where the majority of GGC is bound to whey proteins (serum albumin and lactoglobulin), which protect GGC from degradation.[56]

GGC is also an effective agent in lowering oxidative stress (Figure 1). Neurons are sensitive to excess ROS and require continuous intracellular production of GSH for survival. Under oxidative stress, GGC can effectively replenish depleted GSH levels by regulating the synthesis of GSH. Additionally, GGC can act as a thiol-redox regulator by efficiently detoxifying mitochondrial ROS through GP.[50,57]

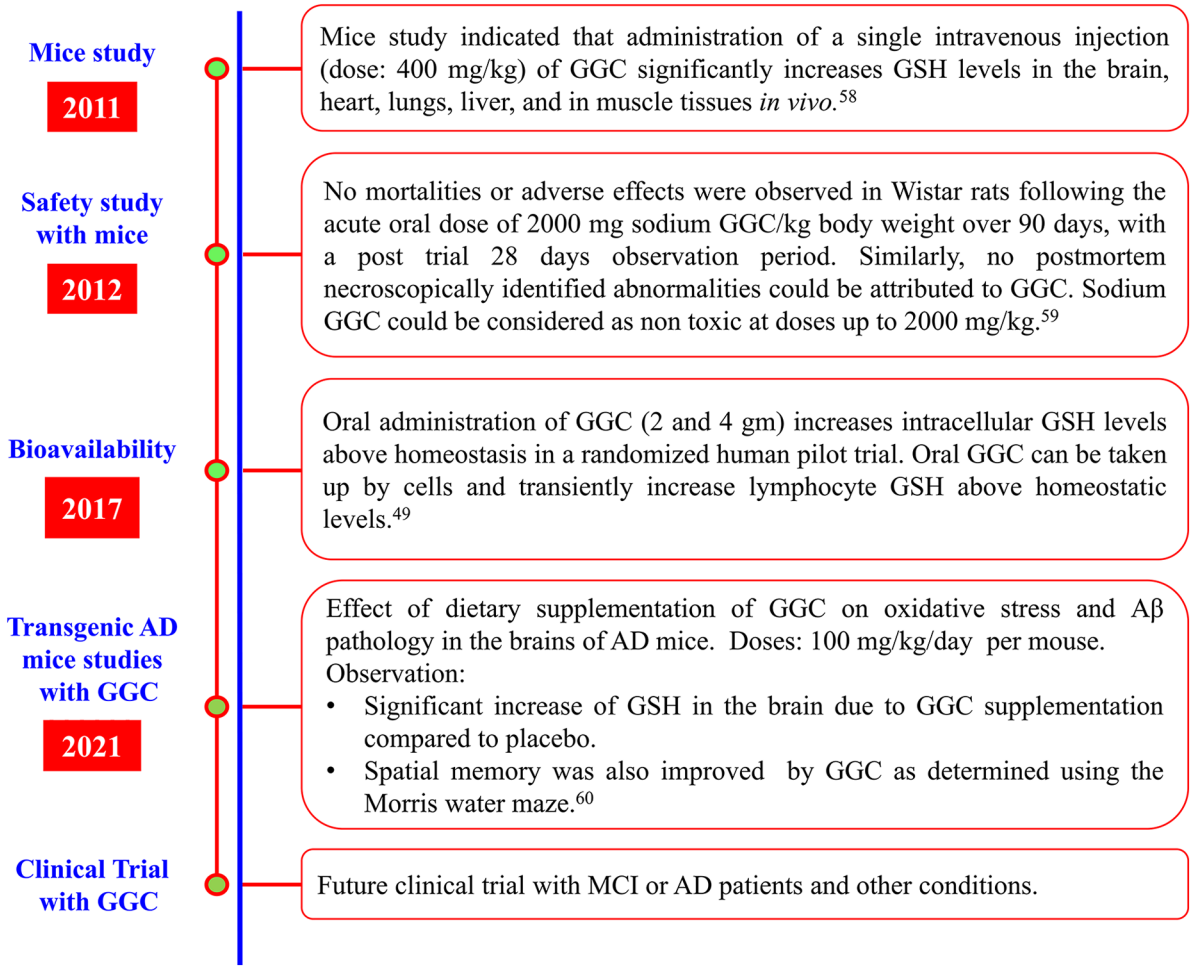
GGC supplementation and safety study on rats and healthy humans

Intravenous injection of GGC to mice significantly increases GSH levels in the brain, heart, lungs, liver, and in muscle tissues.[58] Toxicity studies conducted on rats have demonstrated GGC supplementation to be safe according to the Organization for Economic Cooperation and Development (OECD) toxicology protocols for acute and repeated doses.[59] No mortalities or adverse effects were observed in Wistar rats following the acute oral (gavage) administration of 2000 mg sodium GGC/kg body weight.[59] There was no adverse effect on healthy humans due to supplementation of single oral doses (2 and 4 g) of GGC.[49]

Brain GSH enrichment using GGC

The impact of dietary supplementation of GGC was investigated on APP/PS1 mice to monitor oxidative stress and Aβ pathology. The APP/PS1 mice were fed with GGC (100 mg/kg per mouse per day) or chow (placebo) from 3 months of age until 6 months of age.[60] The biomarkers of apoptosis, cell death, oxidative stress, neuroinflammation, and Aβ load were analyzed. GGC supplementation increased GSH level, lowered brain lipid peroxidation, and lowered brain Aβ load compared to APP/PS1 mice fed a standard chow diet. The spatial memory performance of APP/PS1 mice also improved significantly with GGC supplementation compared to placebo-treated mice.[60] A chronological development involving GGC in preclinical and healthy human study is presented in Table 2.

Table 2. Preclinical studies with GGC in rats, transgenic AD mice, and healthy humans to investigate the toxicity, dosage, and efficacy in AD mice model. There are two ongoing clinical trials to study the impact of GGC on Parkinson's disease patients (NCT07064005) and repetitive head injury patients (NCT07050173).



Future clinical applications involving GGC

There is one report investigating the safety and tolerability of GGC supplementation on MCI patients (Clinical trial ID: NCT07583251). There is an urgent need for a randomized, double-blind, placebo-controlled clinical trial for academic research to assess the efficacy of GGC supplements in MCI patients for brain GSH enrichment and subsequent enhancement of cognitive performance. Upcoming clinical trial with GGC supplementation in psychiatric disorder (schizophrenia) is an immediate interest.[61]

Acknowledgements

Thanks for the funding support from the Chuck Noll Foundation, Robert J Coury Family-Mylan Foundation, Crawford family foundation, and Waste Connections Inc. Appreciation to Ms. Avani Dixit (undergraduate student, University of Pittsburgh) and Ridhima Ghoshal (undergraduate student, University of Pittsburgh) for figure preparation. Thanks to Ms. Nazia Abdul Rasheed Pillar (Clinical Research Coordinator, University of Pittsburgh) for literature search.

Dr. Mandal dedicates this Editorial to honor patients in various clinical studies for their participation and support.

ORCID iDs

Pravat K. Mandal https://orcid.org/0000-0003-4999-2808
George Perry https://orcid.org/0000-0002-6547-0172

Author contribution(s)

Pravat K. Mandal: Conceptualization; Data curation; Investigation; Methodology; Validation; Writing – original draft.
George Perry: Investigation; Resources; Writing – review & editing.
Joseph C. Maroon: Data curation; Resources; Writing – review & editing.

Patricia Corby: Data curation; Methodology; Resources; Writing – review & editing.
Riddhi Patira: Methodology; Resources; Writing – review & editing.
Oscar L. Lopez: Formal analysis; Investigation; Resources; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Waste Connections Inc., Chuck Noll Foundation for Brain Injury Research, Robert J Coury Family-Mylan Foundation, Crawford family foundation.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, financial interest, authorship, and/or publication of this article: George Perry and Pravat K. Mandal are Editorial Board Members of this journal but were not involved in the peer-review process of this article nor had access to any information regarding its peer-review.
The authors declared no conflicts of interest with respect to the research, financial interest, authorship, and/or publication of this article.

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